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10/813,336	03/29/2004	Stephen Grimes	1102865-0046	5110

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EXAMINER	
FOSTER, CHRISTINE E	
ART UNIT	**PAPER NUMBER**
1641	

DATE MAILED: 10/20/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/813,336	GRIMES ET AL.	
	Examiner	Art Unit	
	Christine Foster	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 September 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *14-37* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *14-37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *29 March 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *4/18/05, 7/18/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of Group II, claims 14-37 in the reply filed on July 17, 2005 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Applicant's supplemental response filed September 16, 2005 is acknowledged. Claims 1-13 and 61-80 have been canceled. Claims 14-37 are currently pending in the application.

Information Disclosure Statement

Applicant's Information Disclosure Statements filed 4/18/05 and 7/18/05 have been received.

The information disclosure statement filed 4/18/05 fails to comply with 37 CFR 1.98(a)(2), which **requires a legible copy of each cited foreign patent document; each non-patent literature publication or that portion which caused it to be listed**; and all other information or that portion which caused it to be listed. It has been placed in the application file, but the information referred to therein has not been considered except where indicated on the attached form PTO-1449.

The information disclosure statement filed 7/18/05 fails to comply with 37 CFR 1.98(a)(1), which requires the following: **(1) a list of all patents, publications, applications, or other information submitted for consideration by the Office;** (2) U.S. patents and U.S. patent application publications listed in a section separately from citations of other documents; (3) the

application number of the application in which the information disclosure statement is being submitted on each page of the list; (4) a column that provides a blank space next to each document to be considered, for the examiner's initials; and (5) a heading that clearly indicates that the list is an information disclosure statement. The information disclosure statement has been placed in the application file, but the information referred to therein has not been considered. **Specifically, the copy of the document by Wang et al. was not considered because it was not listed on an Information Disclosure Statement.**

In addition, the references on the IDS submitted 7/18/05 have been lined through, as all of the documents therein were previously listed on the IDS filed 4/18/05.

Specification

The abstract of the disclosure is objected to because the specification refers to a U.S. patent application entitled "Diagnosis and Treatment of gastrointestinal Disease" of T.C. Wang on p. 4, but the patent application number listed is incorrect. The correct patent application publication number is 2003/0049698.

The specification is objected to as failing to provide proper antecedent basis for the claimed subject matter. See 37 CFR 1.75(d)(1) and MPEP § 608.01(o). Correction of the following is required: The claims recite hybridoma cell lines accompanied by ATCC accession numbers, but the listing of the hybridoma cell lines on p. 17-18 of the specification includes blank spaces in place of the accession numbers.

Correction is required. See MPEP § 608.01(b).

Claim Objections

Claims 16, 24, and 28 objected to because of the following informalities: claims 16 and 28 recite "the C-terminal **end**" of gastrin hormones, while the claims from which they depend (claims 15 and 27) recite only "the C-terminal" of gastrin hormones. It is suggested that the claims refer consistently either to "the C-terminal" or to "the C-terminal end".

Claim 24 has no space between the words "23" and "wherein" in line 1.

Claim 27 recites a method of "claim 1 or claim 14"; however, claim 1 is canceled.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 18, 22, 26, 30, and 34 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such as way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The invention appears to employ a novel biological material, specifically the monoclonal antibodies produced by hybridoma cell lines 458-1, 400-1, 400-2, 400-3, 400-4, 401-2, 445-1, and 445-2. Since the monoclonal antibodies are essential to practice the claimed invention they must be readily available or obtainable by a repeatable method set forth in the specification, or otherwise readily available to the public. If the monoclonal antibodies are not so obtainable or

available, the requirements of 35 USC 112, first paragraph may be satisfied by a deposit of the hybridoma cell lines.

The specification does not disclose a repeatable process to obtain the monoclonal antibodies and it is not apparent if the biological material or source materials are both known and readily available to the public.

It is noted that Applicant has deposited the hybridoma cell lines listed above with the American Type Culture Collection on March 25, 2004 under the Accession Nos. PTA-5896, PTA-5889, PTA-5890, PTA-5891, PTA-5892, PTA-5894, and PTA-5895 (see claims 18, 22, 26, 30 and the specification p. 17-18), but there is no indication as to public availability.

If the deposit is made under the terms of the Budapest Treaty, then an affidavit or declaration by Applicants, or a statement by an attorney of record over his or her signature and registration number, or someone empowered to make such a statement, stating that the instant invention will be irrevocably and without restriction released to the public upon issuance of a patent, would satisfy the deposit requirement made herein. In instances where the claimed invention consists of sexually unstable material a deposit of the parental material is required if the parental material is considered sexually stable.

If the deposit has not been made under the Budapest Treaty, then in order to certify that the deposit meets the criteria set forth in 37 CFR 1.801-1.809 and MPEP 2402-2411.05, Applicant may provide assurance of compliance by affidavit or declaration, or by someone empowered to make the same, or by a statement by an attorney of record over his or her signature and registration number showing that:

a. during the pendency of the application, access to the invention will be afforded to the Commissioner upon request;

b. all restrictions upon availability to the public will be irrevocably removed upon granting of the patent;

c. the deposit will be maintained in a public depository for a period of 30 years, or after 5 years after the last request or for the enforceable life of the patent, whichever is longer;

d. a test of the viability of the biological material at the time of deposit (see 37 CFR 1.807); and the deposit will be replaced if it should ever become inviable.

Claims 14-37 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a biological fluid sample that is from a human subject, does not reasonably provide enablement for a biological fluid samples from other sources. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The claims are drawn to a method for determining gastrin hormone in a biological fluid sample using antibodies that selectively bind N-terminal and C-terminal epitopes of gastrin hormone.

The specification discloses that the biological fluid may be any fluid comprising material of biological origin (see the specification, p. 7). Preferred biological fluids include bodily fluids of an animal, especially a mammal, and preferably a human subject. The specification discloses antibodies capable of selectively binding gastrin hormone (e.g., p. 8-9). However, only gastrin

hormones from human are disclosed (p. 1-2; p. 10, "Analytical methods" first paragraph; p. 12-14). Working examples are drawn to determination of human gastrin hormone from human serum or plasma (Examples 1-2 and Table 3). There is no disclosure of gastrin hormone sequences other than human gastrin hormones, or of antibodies that recognize non-human gastrin hormones. There are no working examples of detection of gastrin hormones in biological fluid samples other than human biological fluid samples.

The prior art teaches that the pond snail expresses gastrin/CCK peptides, but that the gastrin/CCK-like snail peptide sequence is different from the vertebrate sequence (Rehfeld et al., "Residue-specific immunochemical sequence prediction" (1994) *Journal of Immunological Methods* **171**:139-142, pages 139-141 in particular). Rehfeld et al. further teach that antibodies that recognize residue-specific sequences of human gastrin hormone do not bind to the snail peptide (p. 140, left column, first full paragraph in particular). Therefore, the antibodies disclosed in the instant application would not necessarily bind to gastrin hormones biological fluid samples comprising non-human gastrin hormones, as antibodies that recognize residue-specific sequences would not bind to gastrin hormones that have different sequences.

Therefore, due to the state of the prior art, the lack of direction/guidance presented in the specification regarding detection of non-human gastrin hormones, the lack of working examples directed to same, and the breadth of the claims, the specification fails to teach the skilled artisan how to make and use the claimed invention in its full scope without undue experimentation.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 14-37 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 14 recites a "N-terminal" and a "C-terminal" of gastrin hormone. Similarly, claims 15-16, 19-20, 23-24, 27-28, 31-32, and 35-36 refer to "N-terminal" or "C-terminal". The terms "N-terminal" and "C-terminal" are indefinite because it is unclear which amino acids of gastrin hormones would be considered within the "N-terminal" and "C-terminal" portions, as the specification does not explicitly define "N-terminal" and "C-terminal."

Claim 14 recites a "biological fluid sample comprising a gastrin hormone from a patient." The sentence structure indicates that the gastrin hormone is from a patient, but it is not clear whether the biological fluid sample is also from a patient.

Claim 14 recites "suitable conditions" in part (c). It is unclear what conditions would be considered "suitable" and what variables might be associated with suitable or unsuitable conditions. Similarly, the claim recites a "suitable detectable marker-conjugated antibody" in part (d). It is unclear whether the suitable antibody referred to is one that selectively binds a C-terminal epitope bound to the gastrin as recited in the claim, or if there are other factors that would render the antibody suitable or unsuitable.

Claim 14 recites an antibody that "selectively binds an C-terminal epitope bound to the gastrin hormone" in part (d). It is unclear whether the epitope is a C-terminal epitope of the gastrin hormone or a C-terminal epitope of some other moiety that is bound to the gastrin hormone.

Claims 21, 25, 29, 33, and 37 recite a monoclonal antibody that "has the characteristics of" a recited monoclonal antibody. The claims are indefinite because it is unclear what characteristics are referred to.

Claims 21 and 26 recite hybridoma 400-2 and 401-2, respectively. The claims are indefinite because the two hybridomas have the same ATCC accession number (PTA-5890).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 14-17, 19-21, 27-29 and 31-33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Goetze et al. ("Impact of Assay Epitope Specificity in Gastrinoma Diagnosis" (February 2003) *Clinical Chemistry* 49: 333-334) in view of Yokoi et al. (US Patent No. 5,643,735) and Berg et al. (*Biochemistry*. Berg, Jeremy M.; Tymoczko, John L.; and Stryer, Lubert. New York: W. H. Freeman and Co.; 2002, Sections 4.3.1-4.3.3 and Figure 4.35).

Goetze et al. teach an ELISA method for determining the amount of gastrin-17 hormone in a serum sample, comprising the steps of obtaining a serum sample from a patient, providing a gastrin-17-specific antibody adsorbed to the wells of a microplate, adding the diluted serum sample to the microplate, adding a second gastrin-17-specific antibody, followed by biotinylated IgG, which bound to the second antibody (p. 333, left column, paragraphs 2-3 to right column, first paragraph; p. 334, left column, lines 3-5). Avidin-labeled horseradish peroxidase was used

for signal production, and after the enzymatic reaction was terminated, the intensity of color was determined by measuring the absorbance at 450 nm and the concentrations of gastrin-17 was determined (p. 33, right column, lines 10-21 and 33-35 in particular).

Although Goetze et al. fail to specifically recite that the serum sample was incubated under suitable conditions for binding of the gastrin hormone to the N-terminal antibody to produce an immobilized complex of the antibody bound to the hormone, such feature would be inherent in the ELISA detection method of Goetze et al. and it would be readily apparent to one of skill in the art that the detection of gastrin-17 by Goetze et al. would involve formation of such an immobilized complex. Furthermore, although Goetze et al. fail to specifically recite that the immobilized complex is incubated with a development reagent, Goetze et al. teach an ELISA method using the detectable marker horseradish peroxidase for signal production as well as color detection by measuring the absorbance at 450 nm. It would be readily apparent to one skilled in the art that the method employed a development reagent that was converted to a colored product detectable at 450 nm, as in classical ELISA techniques (see Berg et al., section 4.3.3, paragraph 1). In addition, while Goetze et al. fail to specifically recite washing the immobilized complex prior to addition of the second antibody and prior to incubation with a development reagent, Berg et al. teach that such washing steps are well known in ELISA methods (Figure 4.35).

With regard to claims 15, 19, 27 and 31, Goetze et al. teach antiserum raised against the cyclized N-terminus of gastrin-17, which detects both gastrin-17 and its C-terminal extended precursors. Goetze et al. also teach antiserum raised against the C-terminal tetrapeptide sequence of all bioactive gastrins (p. 333, right column, lines 1-9).

However, Goetze et al. fail to teach the use of these N-terminal and C-terminal-specific antibodies in the gastrin-17 ELISA method discussed above.

However, Yokoi et al. teach that if one could obtain an antibody that specifically recognizes the N-terminus of a peptide (in this case, thymosin) and another antibody that specifically recognizes the C-terminus of the peptide, then a sandwich immunoassay would be available (column 1, lines 42-53; column 4, line 66 to column 5, line 25). Yokoi et al. further teach that the sandwich method is advantageous from the viewpoint of sensitivity and specificity (column 1, lines 50-53).

Therefore, it would have been obvious to one of ordinary skill in the art employ the N-terminal and C-terminal-specific gastrin antibodies (taught by Goetze et al.) in the ELISA method for determining gastrin hormone of Goetze et al., because Yokoi et al. teach that the use of an N-terminal-specific and a C-terminal-specific antibody together allows for a sandwich immunoassay to be performed, which is sensitive and specific. One would have reasonable expectation of success because Yokoi et al. teach N-terminal and C-terminal-specific antibodies in an immunoassay to detect a peptide, of which gastrin is an example.

Goetze et al. also fail to teach that the antibody that selectively binds a C-terminal epitope is conjugated to a detectable marker: in the method of Goetze et al., the antibody that selectively binds a C-terminal epitope is bound by biotinylated IgG, which is subsequently bound to avidin-labeled horseradish peroxidase. It would be readily envisaged by one skilled in the art that the horseradish peroxidase detectable marker enzyme may also be conjugated to the second monoclonal antibody. For example, Berg et al. teach that in ELISA methods using two different antibodies to a single antigen, the second antibody may be linked to an enzyme capable of

converting development reagent ("substrate") to a colored product, where the rate of color formation is proportional to the amount of antigen (section 4.3.3 and Figure 4.35, part (B) "Sandwich ELISA").

Therefore, it would have been obvious to one of ordinary skill in the art to attach the horseradish peroxidase detectable marker directly to the second antibody, in order to allow for detection of the amount of antigen in proportion to the rate of formation of colored product by the enzyme. One would have reasonable expectation of success because Berg et al. teach attachment of enzyme labels to second antibodies in ELISA methods involving detection of an antigen using two different antibodies, such as the method of Goetze et al.

With regard to claims 16-17, 20-21, 28-29, and 32-33, Goetze et al. also fail to teach monoclonal antibodies or antibodies that have the "characteristics of" the recited monoclonal antibodies. Berg et al. teach the advantage of monoclonal antibodies, which can be obtained in large amounts by the hybridoma method, over an impure mixture of antibodies in that monoclonal antibodies serve as precise analytical and preparative reagents (Section 4.3.2). Berg et al. also teach that antibodies have specific and high affinity for the antigens that elicited their synthesis, and that antibodies recognize a specific group or cluster of amino acids (Section 4.3.1).

It would have been obvious to one of ordinary skill in the art to employ monoclonal antibodies instead of the antiserum in the method of Goetze et al. and Yokoi et al. because Berg et al. teach that monoclonal antibodies are precise analytical reagents that are preferable to an impure mixture of antibodies. Berg et al. also reveal that such monoclonal antibodies would have the characteristics of those monoclonal antibodies recited in claims 17, 21, 29, and 33, in that all

antibodies have specific and high affinity for the antigens that elicited their synthesis, and that all antibodies recognize a specific group or cluster of amino acids.

Claims 22 and 34 are rejected under 35 U.S.C. 103(a) as being unpatentable over Goetze et al. in view of Yokoi et al. and Berg et al. as applied to claims 14-17, 19-21, 27-29 and 31-33 above, and further in view of Grimes et al. (US Patent Application Publication 2002/0058040). Goetze et al., Yokoi et al, and Berg et al. are as discussed above, which fail to teach the monoclonal antibodies produced by the hybridomas 400-1, 400-2, 400-3, or 400-4.

However, Grimes et al. teach anti-hG17 monoclonal antibodies 400-1, 2, 3, and 4 (column 8, lines 4-5) in a method for determining G17 gastrin hormone (paragraphs 25 and 104-125 in particular).

Therefore, it would have been obvious to use the anti-hG17 monoclonal antibodies 400-1, 2, 3, and 4 as taught by Grimes et al. in the method of determining the amount of gastrin hormone of Goetze et al., Yokoi et al., and Berg et al. because Grimes et al. teach that monoclonal antibodies 400-1, 2, 3, and 4 are capable of recognizing human G17.

Claims 23-25 and 35-37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Goetze et al. in view of Yokoi et al. and Berg et al. as applied to claims 14-17, 19-21, 27-29 and 31-33 above, and further in view of Gevas et al. (US Patent No. 5,607,676).

Goetze et al., Yokoi et al, and Berg et al. are as discussed above, which fail to teach antibodies selective for the N-terminal of G34 or Gly-extended G34.

Gevas et al. teach that G34-specific antibodies that specifically target amino acid residues in the amino terminus of G34 (column 6, lines 1-47; Example 1, "Peptide 5" in particular; and column 11, lines 60-65; column 12, Table 2, "Immunogen 5" in particular and lines 50-59). Such antibodies are capable of responding selectively and specifically to G34 but not to G17 or CCK (column 6, lines 2-8).

With regard to claims 24 and 36, Gevas et al. teach that G34 specific monoclonal antibodies may be produced by hybridoma (column 6, lines 43-48). As discussed above, such G34 monoclonal antibodies would have the characteristics of the monoclonal antibodies recited in claims 25 and 37, in particular specific affinity.

Therefore, it would have been obvious to employ the G34-specific monoclonal antibodies that specifically target residues in the amino terminus of G34 as taught by Gevas et al. in the method of determining the amount of gastrin hormone of Goetze et al., Yokoi et al., and Berg et al. order to selectively recognize G34 but not G17 or CCK.

Conclusion

No claims are allowed.

The following is also cited by the examiner as prior art of relevance:

Azuma et al. ("Immunocytochemical evidence for differential distribution of gastrin forms using region-specific antibodies" (1986) *Gastroenterol Jpn* **21**:319-324) teach immunocytochemical staining of different forms of gastrin in tissue samples using antibodies specific to the N-terminus and C-terminus of G17 gastrin.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christine Foster whose telephone number is (571) 272-8786. The examiner can normally be reached on M-F 8:30-5. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le can be reached at (571) 272-0823. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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